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HIGH PRESSURE LIFE LABORATORY AT THE UNIVERSITY OF NORTH DAKOTA--ETC(U)
NOV 77 T K AKERS, W A BARES, D L BECKMAN

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FINAL REPORT

THE HIGH PRESSURE LIFE LABORATORY AT
THE UNIVERSITY OF NORTH DAKOTA
GRAND FORKS, NORTH DAKOTA

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I. INTRODUCTION

Research into the effects of undersea submersion at depths to 1,300 feet is the prime aim of the Man-in-the-Sea Project at the University of North Dakota. It is one of the largest and most advanced research projects of its kind and has the only high pressure life laboratory in the free world capable of studies of the long-term effects of high pressure on the reproduction, nutritional needs and general health of test animals.

Planning and experimentation for the UND Man-in-the-Sea Project have been under way since 1968. The project research already has produced nearly 80 scholarly papers, dissertations and theses. It is funded by the U.S. Office of Naval Research, and is staffed by UND faculty and student researchers from several academic disciplines.

Man-in-the-Sea research deals with a broad spectrum of problems associated with life under high pressure and has wide-ranging possibilities for application. Knowledge gained from the research will be important in developing ways for man to live under the sea for prolonged periods to recover the food and energy resources found there.

The UND research also promises to aid medicine by explaining the reaction of the human body to various gasses, bacteria, drugs and other substances under pressure. Further application of knowledge derived from the project extends to military and defense needs of the country.

The Man-in-the-Sea project occupies a 12-room suite in Upson Hall and six laboratories in the Medical Science Building. A contribution of \$400,000 by UND alumnus Maxwell M. Upson was significant in the development of Upson Hall, which contains College of Engineering laboratories and workshops and those for the Man-in-the-Sea Project. The project's requirements were incorporated into the basic design of Upson Hall. Mr. Upson, a New York construction engineer, has made thousands of dollars in contributions to UND for scholarships and engineering construction.

The major component of Man-in-the-Sea in Upson Hall, the High Pressure Life Laboratory, measures 40 feet long, 20 feet wide and nine feet high and consists of two seven-foot spheres joined by a passageway with a 24-inch gate valve. Each sphere is surrounded by seven 18-inch animal living chambers separated from the main sphere by 18-inch gate valves. To facilitate prolonged study under constant pressure, animals can be transferred to the spheres while the living chambers are decompressed, cleaned and resupplied.

Construction of the test facility became possible when the Office of Naval Research made available as Government Furnished Equipment some 15 pieces of machine tools and welding equipment. The ability of the University to machine and fabricate in-house almost all major components saved several millions of dollars. In addition, items of electronic systems and laboratory instruments obtained from Government Surplus have greatly facilitated the research program.

Pressures of up to 40 times that experienced on the earth's surface can be maintained in the chamber complex. Research calling for exposure to high pressure for prolonged periods of up to two years or more is planned.

THE FACILITIES

The High Pressure Life Laboratory at the University of North Dakota can trace its conceptual beginning back to 1966 when a teacher in the mechanical engineering department needed a design project for his senior students, and a physiologist in the School of Medicine needed a pressure chamber in which to conduct research. Several members of both departments held a series of meetings to explore ways and means of satisfying both needs. The immediate product was a small, double pressure chamber capable of 10 atmospheres of pressure thereby initiating the first bio-engineering efforts at UND.

The first efforts were so fruitful that the group stayed together and continued to discuss design possibilities and biomedical applications of engineering. This was a time of mutual education. First, there were two vocabularies to master--that of the engineer and that of the medical researcher. Neither knew how to speak the other's language. The first year was spent in learning what each discipline had to offer the other.

About this time, the United States Government initiated a program called "Project Themis," designed to create centers of excellence in universities throughout the country. The North Dakota group felt it would be an excellent opportunity to further develop the initial rapport and to develop such a center in hyperbaric science. Additional members were recruited from the College of Engineering and the School of Medicine. They submitted a project proposal which was unsuccessful. However, with one more year of work and weekly meetings, a second more detailed and comprehensive proposal earned approval. The Office of Naval Research was designated the cognitive Federal agency. Thus began the long collaborative efforts between UND and the Office of Naval Research to develop the High Pressure Life Laboratory.

The first chamber was a small 6-inch diameter by 16-inch long 10 atmosphere chamber purchased from Bethlehem Corporation. The second test facility was built on campus and consisted of two chambers: a 16-inch diameter by 24-inch long living chamber connected by a 4-inch gate valve to a 6-inch diameter by a 12-inch long working chamber. This 10-atmosphere chamber was designed to study the behavioral activity of rats under long-term exposure to high pressure. The concept was to keep animals at high pressure for prolonged periods of time, yet enable removal of normal waste products and resupplying of food and water. This concept was partially successful in the first double chamber. The chamber had a gas cleaning system that operated at 1 atmosphere, which required that the contaminated gases be reduced in pressure to 1 atmosphere, scrubbed and cleaned and then recompressed for recirculation. This proved to be inefficient and animals could be maintained in a good state of health for approximately 10 days.

The next attempt was to build a larger chamber, 18 inches in diameter and 36 inches long, which was capable of 40 atmospheres pressure. It had a circulation system which operated at high pressure throughout its entire circuit. Urine was removed from the chamber by special locking devices, and additional water could be added as needed. However, the food supply for the entire experiment was loaded before compression.

Approximately three years went into the design aspects of the entire facility, and for the last two years the construction and updating of the design has taken place. It is indeed fortunate that the College of Engineering was constructing the Upson teaching and research laboratories during this time because the project's requirements were incorporated into the basic design of the Upson Engineering Building.

From the experience gained in the pilot studies, it became apparent that the ideal facility should permit frequent resupply of food and water and removal of waste products without reducing the experimental pressure on the animals. This would necessitate moving the animals to a clean, previously stocked chamber. This concept was pursued and has materialized in the facility being dedicated. It consists of two large 7-foot diameter spheres, interconnected by a 24-inch gate valve. Each sphere serves as the main median lock for seven 18-inch diameter living chambers. Each chamber is connected to the sphere by 18-inch gate valves. The animals are housed in individual cages on sleds that ride on rails in each chamber. The chamber is cleaned by pulling the sled with a remotely controlled tractor onto a turntable in a 7-foot sphere. The turntable is then turned to an empty chamber which has been previously cleaned and supplied with water and food, and the sled moved into the chamber to position the cages in alignment with food and water supplies. Meanwhile, the vacated chamber is isolated from the sphere by closing the 18-inch valve, decompressed, cleaned and resupplied. After restoring the pressure and opening the gate valve, it is then ready to accept another sled of animals. In this manner, animals may be kept at high pressure for indeterminate lengths of time.

Except for a few large items, the entire chamber complex was constructed on the campus in the mechanical engineering and electrical engineering shops. The two 7-foot spheres were fabricated by the Columbiana Boiler Company to our design. The gate valves, quick-open doors, large gas storage tanks, and molecular sieve towers were purchased from commercial sources. However, the rest of the chambers and the entire piping network were all fabricated on campus.

To insure that the animals survive in the test environment, it is also essential that the following experimental parameters be accurately controlled or measured: pressure, temperature, oxygen level, relative humidity and lighting cycle. Since the animals also produce gaseous waste products, the carbon dioxide and other contaminants must be removed from the experimental environment otherwise, the animals would die. It is known that even the normal concentration of nitrogen and oxygen, when compressed to the desired experimental pressures, becomes toxic to animals. This alone necessitated a major design consideration, for it required that the appropriate concentration of oxygen be diluted with a totally inert gas. Helium was selected and constitutes the primary gas used in the facility. Satisfying these constraints resulted in the complex gas circulation and cleansing system.

To be able to determine whether any physiological changes take place and to what extent also required long periods of sustained exposure to the high experimental pressure. This requires the capability to continuously measure and control all the parameters previously listed. It also requires that certain data be taken from the animals themselves. This required developing new techniques and instruments to obtain and record the data. To do this, an IBM 1800 Process Control Computer was selected.

Because many of the processes that were to be controlled by the computer were different from those usually controlled by computers, the hardware that interprets the data coming from the facility to the computer and the commands coming from the computer back to the facility had to be designed and constructed by our own staff. The computer is now installed and is able to maintain the proper environment with only minimum manual intervention.

It is estimated that such a facility constructed in industry would cost approximately \$15 million to \$20 million, but by developing and manufacturing it on the University campus and making it part of the overall research and training of staff members and graduate students, this project has cost only approximately \$1.5 million. More importantly, however, it has afforded invaluable training for numerous graduate and undergraduate students in the College of Engineering and graduate students in the physiology and pharmacology department in the School of Medicine, as well as fostering interdisciplinary cooperation between the departments of mechanical engineering, electrical engineering, physiology and pharmacology, psychology and microbiology. This has engendered many seminars and several graduate courses for further training of students and staff.

Nowhere else in the world can studies on the long-term effects of high pressure on reproduction, nutritional needs and on the general health of animals be undertaken. Studies such as these, done on expendable living tissues of small animals, are invaluable in assessing the effects of high pressure living before man is subjected to them. The High Pressure Life Laboratory is now ready to make these experiments.

During the five years of dreaming, designing and building the facility, the researchers were not idle. Using the first chambers, the physiologists carried on research in various areas of high pressure life support, and during this time many graduate students received high pressure training while pursuing their advanced degrees. Research studies have been completed in a variety of areas. The toxic effects of various combinations of gases have been studied on rats, mice, guinea pigs and chinchillas, and the effects of pressure stress have been assessed on rats. A series of studies was completed, examining the stressors and their effects during decompression upon brain wave patterns, eye movements induced by vertigo and the learning behavior of small rodents.

The nutrition of animals kept in the bizarre environment found in hyperbaric work has been assessed through a long series of nutrition experiments, and the most appropriate temperature to bring the animals to thermal neutrality in these bizarre gas mixtures has been established. Studies of the microbiological changes that take place in this type of environment have begun. Several pharmacological studies have been carried out and are continuing, using the small chambers that eventually were incorporated in the main facility. Obviously, the majority of this

work was done on a short-term (one-to-three day) experimental basis, looking forward to the day when animals can be placed in the hyperbaric chambers, to be maintained from six weeks to two years at pressure.

CHAMBER CAPABILITIES

Pressure Range

Ambient to 1,350 ft. Sea Water
600 lbs./sq. in.
42 kg./sq. cm.
42 ATA

Contaminant Concentrations:

Carbon Dioxide CO ₂	10 ⁵	=1
Carbon Monoxide CO	10 ⁵	=1
Ammonia NH ₃	10 ⁵	=1
Hydrogen Sulfide H ₂ S	10 ⁵	=1
Methane CH ₄	10 ⁵	=1

Pressure Accuracy
=5% of Set Point

Lighting
Variable diurnal lighting cycle

Pressure Set Points

Two independent pressure Set Points, plus compression and decompression

Animal Accommodation

Rat or Guinea Pig Cages:	52
Experimental Control Cages:	24
(2 rats per cage maximum)	

Temperature Range
35° to 122° F
1° to 50° C

Rabbit Cages:	26
Experimental Control Cages:	12
(Cages not presently stocked)	

Temperature Accuracy
10% of Set Point

Data Acquisition

Automatic:

1. Pressure
2. Temperature
3. Telemetry to computer
 - a. Deep body temperature
 - b. Blood pressure

Humidity
40-100% = 5%

Manual:

1. Food consumption
2. Water consumption
3. Urine production
4. Feces production
5. Visual observation

Gas Environment

Diluent: Helium

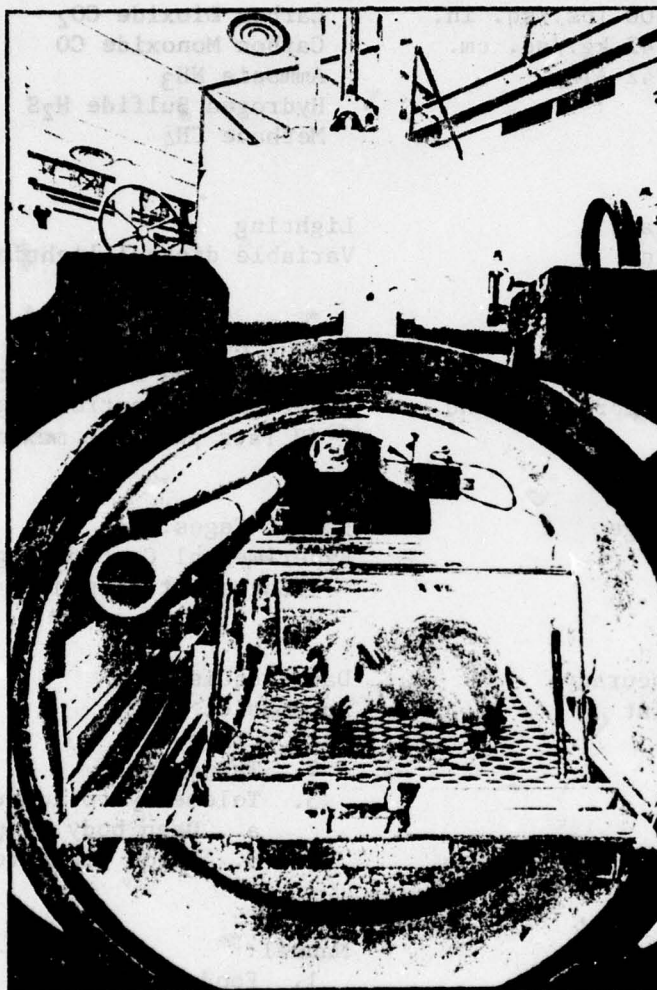
Oxygen Partial Pressure:

0 to 760 mm Hg=20% of Set Point

Experiment Duration

The duration of the experiment, theoretically, will be the life cycle of the test animals. However, major preventive maintenance requirements will limit any single experiment which uses the entire facility to one year.

View of the inside of the experimental chamber
(the animal shown weighs approximately 600 grams).



II. SUMMARY OF EXPERIMENTAL FINDINGS

Metabolic Studies

The effect of helium (He) on brain gamma-aminobutyric acid (GABA) levels was studied in 124 male and 128 female mice. These mice were exposed to He-oxygen (O_2) mixtures at either 1 or 60 atmospheres (atm) for variable periods of time with physiologic O_2 . The mice were compressed to 60 atm for 1 min, 12 hrs, or 24 hrs. After decompression, the brains were removed and GABA levels determined. Significant increases in GABA were found in all mice exposed to He- O_2 at 1 atm, in males at 60 atm for 1 min, and in both sexes at 60 atm for 24 hrs. There was no significant difference in GABA levels between sexes when all groups were considered. Both pressure and the He atm contributed to the increase in GABA.

Although the lung and central nervous system effects of high pressure oxygen in a helium-oxygen (He- O_2) breathing mixture have been investigated, there is a paucity of data concerning the biochemical effects of the He at high pressures. In the present study, a total of 320 mice were exposed for 24 hours to 20, 40, or 60 atmospheres of He- O_2 , with the partial pressure of O_2 maintained within the physiological range of 150-300 mm. Hg. Analysis of brain tissue following decompression showed a linear relationship between the He- O_2 pressure and the increase in gamma aminobutyric acid (GABA) per g of wet brain. The experimental mice showed no adverse effects correlated with the GABA increase; the GABA may have played a role in the apparently normal response of the mice to hyperbaric stress. This study suggests that further investigation of the anticonvulsant properties of GABA might lead to a partial solution of the problems encountered during decompression following deep-sea dives.

The effects of high pressure (HP) helium-oxygen (He- O_2) at physiologic partial pressure (PO_2) on levels of serum alkaline phosphatase (AP), serum lactic dehydrogenase (SLDH), and serum glutamic oxalacetic transaminase (SGOT) were studied in 174 experimental and control female Swiss Webster, Strain C, mice. Animals were exposed to ambient air or He- O_2 at 1, 20, 40 or 60 atmospheres (atm) for 24 hours. No gross changes with HP were observed. SLDH and SGOT activity increased linearly with pressure. There was no change in serum AP. A slight but significant increase in SLDH and SGOT with He- O_2 at 1 atm suggests that He alters cell metabolism or membrane permeability. Mice (8) exposed to 60 atm and sacrificed 2-5 days after decompression showed control levels of SLDH and SGOT. It is concluded that He and/or HP stress may cause slight cell damage or changes in metabolism. The fact that serum enzyme increases were modest and temporary suggests that similar He- O_2 HP environments would be satisfactory for larger mammals and perhaps man.

Nitrogen (N_2) at 7 atm is an anesthetic. Helium (He) was substituted for N_2 in the breathing mixture. This study was to determine the effects of He on the hepatic mammalian glucose-6-phosphatase activity. Ninety-five male and 81 female mice were exposed to He-oxygen (O_2) mixtures varying from 1 to 60 atm for variable periods of time with a physiologic PO_2 . For each sex group, there was an ambient air control group of mice. All N_2 was removed from the chamber with He- O_2 and compressed to 60 atm with He for 1 min, 12 hrs, and 24 hrs. Decompression was at a rate of

0.15 atm per min. The livers were removed and placed in 0.25 M of sucrose at 0° C. Glucose-6-phosphatase activity as P_1 was then determined. Analysis of the data showed a significant increase in the microsomal glucose-6-phosphatase activity in all mice. Glucocorticoid and/or catecholamine increases could have caused the increased enzyme activity. Hepatic glucose-6-phosphate dehydrogenase activity was not increased.

It has been noted by Hamilton and Schaeffer et al., that there was an increase in carbon dioxide (CO_2) tension in the arterial blood (Pa_{CO_2}) of divers even though minute ventilation seemed adequate. Impairment of any one of the several mechanisms by which CO_2 is transported to the lung and eliminated from the body would lead to CO_2 retention and respiratory acidosis. The rapid hydration of CO_2 in the tissue capillaries by erythrocyte carbonic anhydrase and the reverse dehydration in the pulmonary capillaries play a vital role in the CO_2 elimination from the body. Therefore, the CO_2 hydrating capacity of erythrocytes, measured as carbonic anhydrase activity, was studied in mice exposed to 61 atmospheres (atm) of pressure. Groups of mice were placed in a high pressure (HP) chamber for a period of 33 hours (hrs) at either 1 or 61 atm of pressure. The oxygen (O_2) level in the chamber was maintained within the physiologic limits ranging from 150-350 mm. Hg pressure. The maximal pressure was obtained principally by use of helium (He). Control animals were those taken directly from the laboratory cages. The mice exposed to 61 atm were compressed at 0.5 atm per minute (min) and were decompressed at 0.16 atm per min. Blood samples were collected by decapitation, and carbonic anhydrase activity of the erythrocytes was determined. No significant change was detected in the activity of the enzyme. It was concluded by extrapolation that men working in the sea under similar conditions would not significantly retain CO_2 because of an irreversibly depressed function of erythrocyte carbonic anhydrase.

DRUG STUDIES

The effects of helium-oxygen ($He-O_2$) environments were observed upon the pharmacological actions of morphine in male albino rats given 100 mg/kg of body weight. Measurements of 8-h urine volumes revealed that animals maintained in ambient air and $He-O_2$ at 1 ATA exhibited a marked antidiuresis. Animals exposed to $He-O_2$ at 11 ATA showed a normal urine flow when compared with ambient air controls. Uninjected rats maintained in $He-O_2$ at 11 ATA showed a marked diuresis. The study also included experiments to determine whether the excretion of free morphine is altered in $He-O_2$ environments, and whether the analgesic effect of the drug is changed due to $He-O_2$ environments. Exposure to $He-O_2$ at 21 ATA was included in these studies. Significant decreases were noted in the excretion of free morphine during a 24-h period in those animals exposed to 11 and 21 ATA, although no difference was observed in the groups maintained at 1 ATA. Pressure was also shown to decrease the pain threshold in both uninjected and injected animals maintained at 11 and 21 ATA. The results indicate that the metabolism of morphine may be stimulated due to the effects of pressure.

Changes in blood constituents in rats exposed to $He-O_2$ at 1 ATA and 11 ATA after administration of morphine (100 mg/kg) are reported. Injected animals are compared with controls (non-injected) in ambient air and animals subjected to $He-O_2$ at 1 ATA and 11 ATA. Temperature of the chamber was controlled and O_2 partial pressure and CO_2 levels were maintained at standard conditions. After morphine injection the rats were

pressurised and maintained for 4 h before decompression, at which time additional blood samples were obtained. Morphine-injected animals in ambient air showed significant decreases in hematocrit, MCV, glucose, and protein in the blood while showing an increase in the leukocyte count and blood potassium. Noninjected animals maintained in He-O₂ at 1 ATA and 11 ATA showed no deviation from ambient air control animals. Injected animals in He-O₂ at 1 ATA showed no changes from those in ambient air, but animals injected and exposed to 11 ATA did not have a decreased serum protein level or an increase in potassium.

Seventy-two young male Sprague-Dawley rats were fed either an aspirin-supplemented diet or a similar diet without aspirin. Preliminary studies indicated that an oral dose of aspirin, in the form of 1% of the diet, was sufficient to induce the desired gastro-intestinal bleeding. These animals were further treated to controlled environmental exposures. Of the 36 rats fed the aspirin-supplemented diet, 12 rats were exposed to an ambient environment of 1 ATA with room air (pO₂ 159 mm Hg) at a temperature of 28.0-29.0°C; 12 rats were exposed to an environment of 11 ATA with a He-O₂ gaseous mixture (pO₂ 200 ± 15 mm Hg) at a temperature of 32.0-32.8°C; and 12 rats were exposed to an environment of 1 ATA with a He-O₂ gaseous mixture (pO₂ 200 ± 15 mm Hg) at a temperature of 30.0-30.6°C, to account for the possible influences of He-O₂ alone. The variance in environmental temperature was utilized to eliminate the thermal conductive influence of helium, in accordance with the recommendations of Stetzner and De Boer. In all environments, the pCO₂ was held at less than 7.6 mm Hg, and the relative humidity was maintained at less than 40%. A similar protocol was carried out for the 36 rats fed the non-aspirin-supplemented diet. At the end of one, two, and three weeks of exposure, four rats were removed from each experimental condition. At these times, blood samples were collected by cardiac puncture and were measured for blood salicylate levels by the method of Trinder. In addition, several fecal samples, as well as colonic contents, of each animal were measured by the Benzidine test for the presence of blood.

Among the animals fed the aspirin-supplemented diet, the mean blood salicylate levels did not differ significantly from one environmental exposure to another, nor did they differ significantly after one, two, or three weeks of exposure ($P \leq 0.05$). Therefore, the degree of aspirin-induced gastro-intestinal bleeding should not differ from one experimental condition to another, based on blood salicylate levels, unless some other factor is intervening. Although the non-aspirin-fed animals demonstrated intestinal tract bleeding, the degree of bleeding was significantly greater for the aspirin-fed animals ($P \leq 0.05$). However, the intestinal tract bleeding was significantly reduced in the aspirin-fed animals exposed to the 11 ATA He-O₂ environment.

The results indicate that an environment of He-O₂ at 11 ATA protection against gastro-intestinal bleeding induced by aspirin administration. This effect may indicate hyperbaric-induced inhibition of gastric acid secretion, since the prevailing concept for aspirin-induced gastro-intestinal bleeding involves the presence of an acid medium.

ENDOCRINE STUDIES

The effects of long-term hyperbaric exposure on endocrine organ weights

and histology and on epiphyseal-plate width were studied in growing male rats. Six groups of rats were exposed to 21 ATA He-O₂ (200 mmHg O₂), and six groups were maintained at 1 ATA as room-air controls. Each group contained eight rats. At intervals of 2, 3, 5, 8, 10, and 12 weeks, one group was decompressed and studied along with a paired control group. Results indicated no changes in pituitary and adrenal gland weights. Testis weights were variable but histology and sperm content were normal. Only the accessory sex organs decreased significantly in weight; however, prostate and seminal vesicle histology were normal. Tibial epiphyseal-plate width was reduced in 21-ATA groups. These results suggest that long-term hyperbaric exposure has little effect on endocrine organs of the rat and observed weight changes are probably related to the reduced body weights.

Urinary excretion of adrenal cortical hormones was used as an index of stress in laboratory rats and guinea pigs. Experiments were conducted on two strains of adult male rats (Sprague-Dawley, and Holtzman, 255-400 gm) and English short hair guinea pigs (400-600 gm). Twenty-four hour urine samples were collected during control periods in room air (1 ATA) and during exposure to He-O₂ (80-20% at 1 ATA). The animals were then exposed to He-O₂ mixtures at 5, 10, 20, and 30 ATA for 14 hours and were then staged decompressed. The partial pressure of O₂ was kept between 150-275 mmHg during experimental periods. Food and water were available ad lib. and chamber temperature was maintained within the He-O₂ comfort zone (29-30°C, 1 ATA). Unconjugated urinary corticosterone or cortisol, expressed as ug/24 hr. sample was analyzed fluorometrically. Increase pressure showed increased glucocorticoid excretion in both rats and guinea pigs. Excretion values of corticosterone obtained from rats were 1.64 ± 0.25 ; 2.25 ± 0.48 ; 1.87 ± 0.31 ; and 2.71 ± 0.31 at 5, 10, 20 and 30 ATA, He-O₂. Increases in cortisol excretion of 21, 24, 48, and 54%, respectively, were obtained from guinea pigs. Statistically significant differences were found between N₂-O₂ and He-O₂ control samples in rats but not in guinea pigs. Six hour guinea pig samples taken throughout the 24 hour cycle indicated that the greatest excretion was during the decompression phase.

The excretion rate of unconjugated urinary corticosterone collected from male Sprague-Dawley rats (250-400 gm) was used as an index of stress. Twenty-four-hour urine samples were collected during control periods in room air (N₂-O₂) and during exposure to a mixture (80-20%) of helium-oxygen (He-O₂) at 1 atmosphere absolute (ATA). The animals were then exposed to He-O₂ mixtures at 5, 10, 20, or 30 ATA for 14 hours and then stage decompressed. Food and water were available ad lib., and chamber temperature was maintained at $30 \pm 0.5^\circ\text{C}$ at 1 ATA He-O₂. Chamber temperature was increased with pressure up to 33°C at 30 ATA He-O₂. Unconjugated urinary corticosterone was analyzed fluorometrically and expressed as ng/100 gm body weight/24 hours. Statistically significant increases in corticosterone excretion rates were found in He-O₂ control samples above those excretion rates collected in N₂-O₂ samples. Excretion values of corticosterone were increased as much as three-fold over basal values upon exposure to pressure. Urine volume and creatinine excretion both showed general increases with a change to He-O₂ and to increased pressures. Loss of body weight was observed with pressures greater than 5 ATA He-O₂.

Fast Fourier transform (FFT) analysis was performed on levels of 11-hydroxycorticosteroids (11-OHCS) in urinary samples collected from laboratory rats. The control animals were exposed to ambient conditions. The experimental animals were exposed in an experimental pressure chamber to 20 atmospheres absolute of helium and oxygen (20 ata He-O₂). Four 6-hr urine samples were obtained daily and analyzed for the free 11-OHCS content according to the method of Mattingly. The animals were given food and water ad libitum. Marked increases were noted in the excretion rates of the animals subjected to the 20 ata He-O₂ pressure. Using the FFT to calculate the modified power spectrum, a change in periodicity from a diurnal 24-hr cycle to one of 28.4 hrs was obtained.

BONE STUDIES

Bone growth and composition were studied in growing rats following continuous long-term hyperbaric exposure. Six groups of eight rats each were maintained at 21 ATA He-O₂ (200 mm HgO₂) and six groups were kept in simulated test chambers under room-air conditions. One group each of pressurized and control animals were removed and analyzed after 2, 3, 5, 8, 10, and 12 weeks. Each animal was weighed and sacrificed. One femur was removed for fresh, dry, ash, and matrix weight measurement and determination of calcium and phosphorus content. The pressurized animals showed a significant reduction in body-weight gain after each exposure period. Femurs from pressurized animals weighed less than controls but had significantly greater femur/body weight percentages. Calcium and phosphorus content was normal and the ratio of matrix to mineral was unchanged. Results suggest that pressurized animals had accelerated metabolic rates and inadequate caloric intake. However, measurements of bone mineral and matrix content indicate the skeleton develops normally under hyperbaric conditions.

Young male rats were exposed to repeated heliox dives and analyzed for skeletal alterations. Animals were exposed 1, 3, 5, or 7 times to either 1 ATA He-O₂ for 12.5 h, or to 5 ATA He-O₂ for 4 h and a 8.5 h decompression, or to 5 ATA He-O₂ for 4 h and a 1.5 h decompression. In a separate study, 30 rats were exposed 6 times to 5 ATA He-O₂ and explosively decompressed. Animals were sacrificed 20 d after the last dive. There were no significant changes in femur wet weight, density, ash weight, length, or mineral content. Plasma calcium, phosphorus, and alkaline phosphatase remained normal. Eighteen of 30 animals survived the six explosive decompressions; however, there were no significant changes in bone. These results indicate that the number and rate of decompressions used in this study have no lasting effect on bone growth and mineral composition in the rat.

NUTRITION STUDIES

The effect of helium and oxygen at ambient and 21 atmospheres absolute (ATA) upon feed digestibility and utilization was studied. Three groups of growing male guinea pigs were fed Ried-Briggs diet and subjected to environments of air and helium-oxygen at ambient pressures and helium-oxygen at 21 ATA. Substituting helium for atmospheric nitrogen at ambient pressures did not affect feed consumption, digestibility, or growth. When subjected to 21 ATA, the guinea pigs ate 30% less dry matter and grew 137% slower than at ambient pressure conditions. Thus, the efficiency of feed utilization was suppressed 151%. The apparent digestibility of

dry matter, protein, fat, carbohydrates, and minerals was unaffected by the elevated environmental conditions. Heat loss and other non-defined stresses associated with pressure or helium and oxygen at elevated pressure were responsible for halting growth and depleting body tissues.

A 24-d growth study was conducted on rats exposed to ambient air, 11 ATA He-O₂ or 21 ATA He-O₂ conditions. The rats were fed either a standard diet or the standard diet supplemented with 25, 50, or 100% increase of all vitamins, or the last with an additional 50 or 100% increase of casein. Fat, as cod liver oil, was increased 0.5, 1.0, or 2.0% of the diet as the vitamins were increased. The vitamin and fat-supplemented diets, with or without supplemental casein, were adequate to support normal growth of the rats exposed to 11 ATA but not 21 ATA He-O₂ conditions. Urine excretion and water consumption were closely related and varied in accordance with the adequacy of the diet. Feed digestibility was not a limiting factor in determining the growth of the rats under the three environments. The composition of the rat carcasses varied minimally.

A growth study was conducted of rats continuously exposed for 4 weeks to ambient air, 1 ATA He-O₂ or 11 ATA He-O₂ conditions and fed one of 16 diets. The diets were the standard diet alone (adequate according to National Research Council Standards); the standard diet with additional casein (50%), fat (25%), and all vitamins (25%); or the standard diet with all vitamins (25%), or all vitamins increased (25%) except one, which was supplied at the standard level. The standard diet was inadequate to support a normal rate of growth when fed under 11 ATA He-O₂ conditions. Supplemental casein, fat, and vitamins or all vitamins² alone adequately provided nutrients necessary for a normal rate of growth by hyperbaric exposed rats. The standard levels of thiamine, pantothenic acid, biotin, and vitamin K were inadequate and the standard levels of niacin, and vitamins A, D, and E were marginal in supporting growth when fed under hyperbaric conditions.

Exposure to hyperbaric-hyperoxic environments has been reported to alter body weight. Growing guinea pigs were exposed to 20 and 40 ATA with pO₂ levels of 200 and 600 mm Hg for 2, 4, and 6 days, and compared with air controls. Body weight and individual tissue water content were recorded for each animal. The control group of animals averaged gains in body weight, while the treated animals all lost weight. The life span adrenal glands of the treated animals showed alterations in water content after treatment, while the same treatment did not alter the water content in skin, muscle, bone, brain, blood, and heart.

THERMAL STUDIES

Changes in temperature, heart rate, and respiration rate were recorded for control rats at 1 ATA in air at 76° F or He-O₂ at 86° F, and for experimental animals in He-O₂ at 86° during compression to 41 ATA, maintenance at this pressure for 4 hours, and decompression. Comparisons showed that surface, subcutaneous, and rectal temperatures decreased during compression but returned to normal upon decompression. Heart rate, respiration rate, O₂ consumption increased during exposure and returned to normal levels when the animals were decompressed. In a second experimental group, core temperature was maintained at the control level by increasing the chamber temperature to approximately 94° F during compression, maintaining it at this level during exposure to 41 ATA, and decreasing the chamber temperature during decompression. When the precompression

core temperature was maintained, other temperature parameters, heart and respiratory rates, and oxygen consumption remained at control levels. Weight increase for rats in He-O₂ at 1 ATA was less than for the air controls. Rats exposed to 41 ATA with variable chamber temperature lost weight during the experiment, but less than those maintained at 86° during exposure to 41 ATA.

RED CELL FRAGILITY

Recent observations on human red blood cells subjected to two and three atmospheres of pressure indicate an alteration, either mechanical or chemical, within the RBC, leading to distortion and hemolysis. The hemolysis, checked by the RBC fragility test with hypotonic saline, is apparently concomitant with the degree of pressure used and more specifically with the gaseous composition of the atmosphere.

This preliminary study using dog blood is concerned with quantitative and qualitative dog RBC changes at 0 psig (1 atm.), 68 psig (5 atm.), and 135 psig (10 atm.), using 90% helium and 10% ambient atmosphere mixtures. Results on RBC subjected to the above respective pressures for predetermined times and drawn from the chamber have shown that increased helium pressures make dog RBC susceptible to hemolysis when placed in NaCl solutions ranging from 0.50% to 0.28% concentration. Observations have shown that a shift of the normal range curve occurs at higher than atmospheric pressures under the influence of hyperbaric helium. However, the exact nature of the cause for hemolysis changes is not understood.

NYSTAGMUS

Post-rotatory electronystagmograms were recorded from 11 adult male guinea pigs exposed to room air, 1 ATA helium and oxygen (He-O₂), 10 ATA He-O₂, and during decompressions at one of six different decompression rates (0.04, 0.06, 0.08, 0.10, 0.12, and 0.15 ATA/min). Records were analyzed for total number of beats, duration, and frequency. All eye movements were monitored to determine the occurrence of spontaneous nystagmus. Statistically significant alterations in the parameters measured were evident only during decompression and became more frequent during rapid decompression. Spontaneous nystagmus was nonexistent during hyperbaria and slow decompression but was present in all animals exposed to rapid decompression.

EFFECTS OF VARIOUS GASES

Rectal temperature (R.T.), heart rate (H.R.) and respiration rate (R.R.) were recorded for control rats at 36 psi (absolute) N₂-O₂ and for experimental nitrous oxide (N₂O) groups with dilutions of 7, 14, and 21 psi. (Total exposure at 36 psi was 4 hours, and chamber temperature was 86° F.) R.T. showed little change. Slight increases in H.R. occurred with 7 and 14 psi N₂O and were maximal with 21 psi. There was no difference in R.R. and 7 psi, but significant increases at both 14 and 21 psi. O₂ consumption showed increases of 20% at 7 and 40% at 14 psi but little change at 21 psi. A slight increase in activity was observed at 7 psi. A decrease in coordination and an increase in irregular bursts of activity were observed throughout the four hours of exposure at 14 psi. Animals subjected to 21 psi N₂O were anesthetized (AD₁₀₀). All animals recovered rapidly upon removal of the N₂O by decompression and flushing with N₂-O₂.

Male Sprague-Dawley rats were exposed to 13 or 26 Ata N_2 or He in 10, 8, 5, 3, and 2 Ata O_2 (Series I), or 26 Ata inert gas with 0, 25, 50, 75, and 100% in N_2 in 3 ATA O_2 and with He as a diluent (Series II). Rat tolerance was measured by observing each group's LD_{100} , and lung damage was measured by drying the rat lungs to obtain total water values. The present Series I experiments have demonstrated conclusively that an O_2 -inert gas synergism occurs in rats in a hyperbaric environment, and that in rats this synergistic effect is caused by O_2 - N_2 and also by O_2 -He. The synergistic effect of He is unexpected in view of its narcotic potency. Lung damage in the .13 Ata N_2 and He exposed animals increased at the higher O_2 pressures, but the lung damage of the 26 Ata N_2 and He exposed animals was not different from O_2 control values at the higher O_2 pressures. Series II results indicate a gas density dependence on rat survival in 26 Ata N_2 -He mixtures in 3 Ata O_2 ; as the N_2 concentration was increased, rat survival time decreased linearly. At the increased N_2 concentration, lung damage increased progressively.

Male Swiss Webster mice, weighing 25 gms, were exposed to oxygen from 11 to 2 ATA. At least two groups of ten mice were poisoned by oxygen at each pressure to establish an LD_{100} . Decompression, followed by lung water measurement, was accomplished immediately after obtaining each LD_{100} . A second series of oxygen exposures was performed on an equal number of mice pretreated with 30 mgm/kg sodium pentobarbital. The two functions of mean survival times versus oxygen (11 to 2 ATA) were exponential and not significantly separated. The death times for mice given sodium pentobarbital were shorter than nontreated animals at oxygen pressures below 5 ATA. Respiratory depression coupled with lung failure is an explanation for this finding. Lung water in non-treated and sodium pentobarbital-treated animals was significantly elevated ($P < .001$) in all oxygen exposures above control values. At 6 and 7 ATA, there was a significant difference in lung water content between normal and sodium pentobarbital pretreated mice exposed to oxygen.

Males and females of *Chinchilla laniger* were weighed (average 448g), sorted into mixed groups, and subjected to hypoxic or hyperoxic conditions in a pressure chamber previously described. Guinea pigs (average weight 1180 g) of both sexes were exposed to the same conditions.

When subjected to progressive hypoxia, the chinchilla survived longer and at lower PO_2 levels than did guinea pigs of about the same size. Possibly the smaller but more numerous red blood cells in the chinchillas accounted for their greater tolerance to hypoxia. In hyperoxic exposures, no differences in survival times were found in the two species. Fluid shifts from blood to lungs were indicated by the rise in Hct and lung weight increases in both groups of animals.

Lungs from adult guinea pigs exposed to 1 ATA He- O_2 with 200 mm HgP_{O_2} and 20 ATA He- O_2 with 200, 400, and 600 mm HgP_{O_2} were studied with scanning electron microscopy. The appearance of normal alveoli is described. Even before pulmonary O_2 toxicity became symptomatic, subtle changes occurred in the alveoli, such as an increase in macrophages and a marked increase in length of alveolar type-II cell microvilli. These changes occurred in animals exposed to 400 mm HgP_{O_2} , heretofore considered below toxic levels. With increased toxic involvement, the number of alveolar type-II cells increased. A thick layer of material appeared in some of the alveoli, obscuring the Kohns pores and type-I and -II cell sur-

faces. The alveolar-capillary network with underlying erythrocytes was no longer observable. Lungs with the greatest toxic involvement possessed large numbers of macrophages encompassed by a fibrin-like matrix. The alveolar walls were broken down in many instances, and the alveoli were no longer discrete units but took on the appearance of an amorphous mass of lung tissue.

It is well known that sympathetic stimulation, head injury, and hyperbaric-hyperoxic exposure produce pulmonary edema which can be altered by catecholamine blockade. Less well understood are the microstructural changes involved in the lung alveoli during these processes. The ultrastructure of guinea pig lungs was examined, using both SEM and TEM to assess the protective action of both blockade and depletion of catecholamines upon the alveolar alterations induced by hyperbaric-hyperoxic environments. Guinea pigs were exposed to three environments (1 ATA air; 1 ATA heliox, $pO_2=500$ mm Hg; and 20 ATA behiox, $pO_2=500$ mm Hg) for periods of 2, 4, and 6 days. The animals were decompressed, anesthetized, and had the trachea cannulated. The lungs were perfused with glutaraldehyde for 4 hrs and then prepared for SEM or TEM. Non-drug treated animals exposed to hyperoxic conditions had alveoli engorged with macrophages and fibrin, and the lungs appeared grossly liverlike at 6 days. Reserpine-induced depletion rendered protection but severely dehydrated the animals. Dibenzylamine blockade ameliorated the condition somewhat, but alveolar thickening was still present.

Six-day exposure of guinea pigs to a 20 ATA He-O₂ environment containing 500 mm Hg O₂ will produce death in 25% of the animals and pulmonary congestion and edema in the rest. SEM clearly show that the alveoli of the effected animals are engorged with macrophages and fibrin, and the lungs grossly appear hepatic. The lung weight/body weight ratios and wet/dry lung ratios are increased. Reserpine-induced catecholamine depletion prior to and during exposure significantly decreased these effects. Compliance measurements on lungs of animals exposed to hyperoxic-hyperbaric conditions decreased significantly while reserpine treatment restored the compliance to normal or slightly above normal levels. Total lung protein, cholesterol levels and lung weight are increased. Reserpine and dibenzylamine induced sympathetic blockade prior to and during exposure significantly decreases these effects, but potentiates lung wet and dry weight increases. At the same time body weight is decreased in animals exposed to hyperoxic-hyperbaric conditions. These results indicate the involvement of the sympathetic nervous system in the development of hyperoxic-hyperbaric induced pulmonary oxygen poisoning at subconvulsive oxygen tensions.

Lung c-AMP has been shown to rise significantly (five fold) in lungs treated with epinephrine (Palmer, G.C. Biochem. Biophys. Actas, 252: 561, 1971). Measurements of c-AMP from lungs of guinea pigs exposed for 6 days to 1 ATA or 20 ATA He-O₂ environment containing 500 mm/Hg (which produces pulmonary congestion and edema as verified by lung weight ratio and transmission electron microscopy and scanning electron microscopy) increased slightly, 1.5 pmole c-AMP/mg protein to 3.7 pmole c-AMP/mg protein. This increase was reversed when the animals were pretreated with reserpine or dibenzylamine. These results have provided evidence that catecholamines play a role in pulmonary congestion induced by hyperoxic-hyperbaric environment and such an effect is presumably not achieved through

the mediation of c-AMP.

White single-comb Leghorn eggs were incubated in a pressure chamber for 10-day periods at either 10 atm N_2 - O_2 , 10 atm He- O_2 , 2.5 atm air, or 2.5 atm He. During the experiments the O_2 was kept at 150-400 mm Ig. After decompression and blood analysis of the embryos, it was found that 10 atm N_2 - O_2 inhibited viability and development even though 100% of the eggs were fertile. Ten atm He did not prevent partial development, but all embryos were dead. The 40% of the embryos which had developed were alive. 13% were developed but dead. 13% were fertilized only, and 14% were not fertilized. The embryos incubated under 2.5 atm air weighed 27.8% less than controls and possessed 8.1% greater Hb, 20% greater MCHbC, and 26.4% greater MCHb. At 2.5 atm the experiment was inconclusive in assessing nitrogen's role as a growth inhibitor, as seen at 10 and 2.5 atms.

NEURAL STUDIES

Adult, male Sprague-Dawley rats were divided into groups of 10 and pretreated daily for 3 d with drugs known to alter adrenergic function. Half the animals were exposed to OHP (5 ATA O_2 -13 ATA He) for 30 min. The rest were exposed to a mixture of 20% O_2 -80% He at 1 ATA for 30 min. Total lung water contents were compared following experimental exposure. Groups pretreated with phentolamine, reserpine, and a combination of phentolamine, propranolol, reserpine, imipramine, and tyramine had significantly less lung water than controls following OHP exposure. Groups pretreated individually with tyramine, cocaine, imipramine, and propranolol showed no significant reduction in lung water content following OHP exposure. No animals exposed experimentally at 1 ATA showed any signs of pulmonary damage. It is concluded that α -adrenergic blockade and peripheral catecholamine depletion have protective value in preventing pulmonary damage during OHP exposure. Changes in pulmonary capillary hemodynamics appear to be a causal factor in production of OHP-induced lung damage.

In analyzing the effects of hyperbaric helium-oxygen on alpha and beta adrenergic receptors of rabbit duodenum, morepinephrine latency was found to vary directly and linearly with the increase in pressure. This relationship is described by the equation $Y = 9.114 + .905x$. Increasing pressure had no significant effect upon the drug induced change in magnitude of smooth muscle contractions. Pressure does not effect contractile depression by norepinephrine or phentolamine. Alpha receptor blockade by phentolamine was optimal at 10 ATA. Beta receptor blockade with propranolol was maximal at 30 ATA.

Adult male guinea pigs (900 \pm 200 gm) were used in this study. Each animal was sacrificed by a sharp blow to the skull, the chest rapidly opened, and the aorta cannulated using the Langendorff technique. The coronary system was perfused with Chenoweth's solution which had previously been equilibrated with a mixture of 90% O_2 -10% CO_2 and with ambient gas while inside the hyperbaric vessel. The heart with cannula attached was rapidly transferred to an Anderson-Craver coronary perfusion apparatus which had been modified for hyperbaric exposure. Temperature of the perfusate was maintained at 40 \pm 2° C throughout the experimental procedure and was continuously monitored by a telethermometer. Coronary effluent was returned to the perfusate reservoir for recirculation by means

of a roller pump. Heart rate and isometric contractile force were measured with a force displacement transducer connected by a hook to the apex of the heart. The rate of coronary outflow was monitored by a drop counter. Recordings of heart contractions and coronary outflow were made with a Grass Model 79 Polygraph.

The perfusion apparatus was placed inside an upright hyperbaric vessel capable of withstanding internal pressures up to 40 ATA. The chamber was flushed with a 20% oxygen-80% helium gas mixture prior to pressurization with helium. Experimental trials were performed at 1 ATA, 20 ATA, and 40 ATA. The ambient pO_2 was maintained within the physiological range of 155 ± 10 mm Hg, as determined by gas chromatography.

Norepinephrine (5.0×10^{-7} gm), isoproterenol (1.5×10^{-6} gm), and propranolol (1.0×10^{-5} gm) were sequentially injected into the coronary perfusion system by remote control. Heart rate, isometric contractile force, coronary outflow rate, drug latency, and duration of drug response were the parameters observed. The response of each heart to the pharmacological agents was studied at a single pressure level.

Control heart rates were significantly faster at both 20 ATA and 40 ATA than at 1 ATA, indicating an accentuation of sinus nodal discharge during hyperbaric exposure. The positive inotropic response which followed administration of isoproterenol was significantly greater at 1 ATA than at either 20 ATA ($p \pm .05$) or 40 ATA ($p \pm .01$).

In addition, a highly significant decrease in contractile force ($p \pm .01$) below 1 ATA values was noted in response to beta adrenergic blockade with propranolol at 40 ATA.

Following infusion of isoproterenol during beta adrenergic blockade, the positive inotropic response at 40 ATA was significantly less ($p \pm .05$) than the same response at 1 ATA.

In each of the preceding situations, a statistical comparison of control recordings at the three pressure levels showed the same differences as the drug-treated groups. Therefore, the direct effect of hyperbaric exposure of contractile tension development in isolated hearts may be of greater significance than the combination of pressure and neuroeffector drugs in these instances.

Nerve and muscle compound action potentials were measured in the frog sciatic nervegastrocnemius muscle preparation in a hyperbaric helium-air environment. Helium pressure to 60 ATA induced a reversible depression in muscle compound action potential amplitude without significantly affecting other parameters. Blockade induced by Tetraethylammonium while at pressure could be partially reversed upon decompression. A desensitization type of neuromuscular block produced at pressure following Heostigmine infusion could likewise be partially reversed upon decompression. These results suggest a possible involvement of the acetylcholine receptor complex in pressure induced depression of synaptic transmission.

DECOMPRESSION STUDY

A quantitative and predictable approach to decompression has been tested. Decompression profiles were simulated by Continuous System Modeling Program on an IBM 370 digital computer. The gas transfer model consisted of seven tissue compartments in parallel with the nature of gas movement in each compartment described by a resistance-capacitance circuit. Male rats and male guinea pigs were subjected to saturation decompression at 10, 11, 20, 21, 30, 31, and 40 ATA He-O₂. A nomogram was developed which yields for the simulation model, appropriate compartmental-ambient gas differential ratio for a given animal weight and depth of dive. The bends-threshold for maximum-free ascent was determined in male guinea pigs subjected to 11, 21, and 31 ATA.

Complete details of each of the above summarized studies can be found by consulting the appropriate reference in the list of publications which follows.

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APPENDIX

Doctor of Philosophy Dissertations

Bitter, R.A. 1971. Comparative adrenocortical responses of laboratory rats and guinea pigs exposed to normal and hyperbaric environments.

Keefner, K.R. 1971. Some effects of hyperbaric oxygen on the developing chick embryo.

Thompson, R.E. 1971. The effects of oxygen, nitrogen, and nobel gas influences on rat survival at high pressure.

Cromer, J.A. 1972. Comparative measurements of the central nervous system in the rat exposed to normal and hyperbaric conditions.

Reinke, R.L. 1972. The influence of succinate on brain gamma-amino-butyric acid levels in mice and the resulting tolerance to high pressure oxygen.

Stetzner, L.C. 1972. Physiology of the rat in environments of helium, nitrogen, and nitrous oxide.

Hammond, R.E. 1974. Effects of adrenergic neuroeffector drugs on isolated mammalian hearts during hyperbaric exposure.

Jensen, C.B. 1974. The effects of ototoxic and centrally acting drugs on the vestibulo-ocular reflex arc in guinea pigs.

Brennan, D.M.A. 1975. The measurement and analysis of oxygen consumption in scuba divers at 1 ATA, 2 ATA, and 3 ATA of open water while breathing various mixtures of N_2-O_2 , $He-O_2$, and $He-N_2-O_2$.

Boerboom, L.E. 1975. Cardiac output and its distribution under hyperbaric conditions.

Ross, B.K. 1975. Effects of long-term hyperbaric oxygen exposure on lung tissue: An ultrastructural evaluation.

Syftestad, T.T. 1976. Effect of hemorrhage on blood flow to marrow and osseous tissue in conscious rabbits.

Bergren, D.R. 1976. Adrenergic blocking agents and their effects upon lung compliance and surface tension during increased sympathetic activity.

APPENDIX

Master of Science Theses

Reinke, R.L. 1969. A study of the activity of erythrocyte carbonic anhydrase exposed to a high pressure gas environment.

Ritter, T. 1969. The effects of high pressure helium-oxygen atmosphere on mice serum lactate dehydrogenase, glutamic oxalacetic transaminase, and alkaline phosphatase.

Thompson, R.T. 1969. Tolerance of mice to increased oxygen and nitrogen pressures: Design of a dual high pressure chamber.

Dandekar, A.J. 1969. Analog to digital conversion.

Sherry, S.J. 1970. Changes in whole blood stored at various temperatures and in various gaseous environments.

Stetzner, L.C. 1970. Thermal regulation and cardiorespiratory responses in the rat exposed to controlled hyperbaric environment.

Chen, Chen-Jen. 1970. Design and analysis of an implantable biotelemetry system.

Hodges, D.W. 1970. An application of pattern recognition techniques to animal activity measurement.

Nettar, D.R. 1970. Process control instrumentation: Project Themis.

Stearns, B. 1970. Direct digital control of a mass spectrometer.

Orchuk, K. 1970. The design of a life support circulation system for hyperbaric chambers.

Morales, J. 1970. Design of a quick-opening closure.

Saldana, L.N. 1971. Process interface and backup system for a direct digital controller.

Siska, J.C. 1971. Humidity control for test chambers of a high pressure life laboratory.

Wetherbee, J.L. 1971. The design of a gas conditioning system and a gas scrubbing system for a hyperbaric environmental research center.

Master of Science Theses (Cont'd)

- Stites, D.A. 1971. Modification of a spectrophotometric method for assaying caffeine and its use in determining the effects of high pressure environment on caffeine levels of blood and urine in mice.
- Carlson, L.D. 1972. Some effects of hyperbaric He-O₂ on cholinergic receptors.
- MacCarter, D.K. 1972. The effects of hyperbaric He-O₂ on alpha and beta receptor-drug interaction.
- Allen, D.M. 1972. Behavior of rats modified by temperature and helium-oxygen hyperbaria in a simulated dive.
- Olson, R.E. 1972. Isolation and protein analysis of pulmonary surfactant from rat lung.
- Erickson, D.C. 1972. A means of graphical to analog conversion of polygraph recordings.
- Schneider, J.A. 1972. An implantable biotelemetry system for the measurement of blood pressure wave forms.
- Jensen, C.B. 1973. An electronystagmographic study of post-rotatory nystagmus duration, number of beats, and frequency in 10 atmospheres absolute helium and oxygen and during decompression.
- Geiger, J.D. 1974. Effects of hyperbaric conditions on drug metabolizing enzymes and cellular respiratory activity.
- Syftestad, G.T. 1974. Skeletal response of rats to repeated short-term and continuous long-term hyperbaric helium-oxygen exposure.
- Bergren, D.R. 1975. The effects of head injury and high pressure oxygen on pulmonary surface tension.
- Crittenden, D.J. 1975. Effects of oxygen toxicity on heart rate, pressure pulse amplitude, and respiration rate in unanesthetized guinea pig.
- Sexton, J.D. 1975. The effect of sympathetic nerve stimulation on alveolar surfactant.
- Tofano, M.E. 1975. The effects of hyperbaria upon the action of morphine in rats.

Master of Science Theses (Cont'd)

Nelson, D.B. 1975. Distribution of cardiac output in guinea pigs following decompression from 12 days exposure to 21 ATA He-O₂ at 400 and 200 mm Hg oxygen.

Pakola, H.A. 1977. The effect of hyperbaria upon aspirin-induced gastrointestinal bleeding.

Isler, J.R. 1977. Dietary requirements of subjects exposed to hyperbaric He-O₂ conditions: Effects of supplementation of vitamins and/or casein.

Whitley, D. 1977. The effect of adrenergic blocking and catecholamine-depleting agents upon normoxic and hyperoxic animals' pulmonary function tests.

Muza, S.R. 1977. Biochemical effects of adrenergic blocking and catecholamine depleting agents upon hyperoxic-hyperbaric induced pulmonary edema.

APPENDIX

Senior Honors Theses

Drexler, D.E. 1971. Transmitter size reduction and a computer algorithm for data interpretation of transmitted temperature information.

Wendschlag, D.D. 1971. Analysis and control of flow noise and sound reverberation in hyperbaric chambers.

Kosel, G. 1975. The effect of 2- and 4-day exposure to hyperoxic-hyperbaric environments up to 40 ATA upon the growth and tissue water content in guinea pigs.

Mason, M.J. 1976. The effect of hyperbaric and hyperbaric-hyperoxic environments on the growth and tissue water content of guinea pigs.

Thureen, P. and C. Johnson. 1977. The effects of hyperbaric and hyperoxic conditions on the developing chick embryo.